REMARKS

Status of Claims and Amendment

Claims 6, 9, 10, 11, and 17-20 have been amended. Claims 1-5, 7-8, and 12-16 have been canceled. New claims 21-42 have been added. Claims 6, 9, 10, 11, and 17-42 are all the claims pending in the application.

Claims 6, 9, and 10 have been amended to incorporate the limitations of claim 1.

Claim 11 has been amended to be dependent on claim 9, and to even further clarify that the "contacting step is carried out without preheating the subject at 90°C or more." Support for the amendment to claim 11 may be found, for example, at page 6, lines 34-35 of the specification.

Claims 17-20 have been amended to be dependent on claim 6.

In addition, claim 17 has been amended to recite "exhibiting an activity of 2 U/g or more as the activity of digesting a protein highly resistant to denaturation and degradation which is determined as an activity of digesting keratin azure." Support for the amendment to claim 17 may be found, for example, at page 5, lines 19-24 of the specification.

Claim 18 has also been amended to recite "derived from a microorganism belonging to genus *Bacillus*." Support for the amendment to claim 18 may be found, for example, at page 5, lines 27-28 of the specification.

Claim 19 has been further amended to recite a Markush group from which the claimed enzyme may be selected. Support for the amendment to claim 19 may be found, for example, at page 5, line 31 to page 6, line 6 of the specification.

Claim 20 has been amended to even further clarify that the protein that is highly resistant to denaturation and degradation is "a pathogenic prion protein." Support for the amendment to claim 20 may be found, for example, at page 3, lines 24 and 35-36 of the specification.

Support for new claims 21-30 and 35-42 may be found, for example, at page 6, lines 29-30 and lines 34-35 of the specification.

Support for new claims 31-34 may be found, for example, at page 5, lines 21-24, and 27-28, and page 5, line 31 to page 6, line 6 of the specification.

No new matter is added.

Information Disclosure Statements

Applicants thank the Examiner for returning signed and initialed copies of the PTO Forms SB/08 that accompanied the Information Disclosure Statements filed April 10, 2007, and May 25, 2007. Applicants respectfully request that the Examiner return signed and initialed copies of the PTO Forms SB/08 that accompanied the Information Disclosure Statements filed April 25, 2005, and July 18, 2005.

Claim to Priority

Applicants thank the Examiner for acknowledging Applicants' claim of priority to Japanese Application No. 2002-309248, filed October 24, 2002, as well as receipt of the certified copy of the priority document.

Election/Restrictions

On page 2 of the Office Action, the Examiner acknowledged Applicants' election with traverse of Group I, upon which claims 1-3, 5, 6, 8, 13-18, and 20 are readable. However, in view of Applicants' traversal arguments submitted December 4, 2007, Applicants appreciate that

the Examiner has withdrawn the requirement for restriction. Accordingly, claims 1-20 have been examined on the merits.

Response To Rejection Under 35 U.S.C. § 101

Claim 7 was rejected under 35 U.S.C. § 101 because the claim allegedly fails to set forth any steps involved in the process. The Office Action asserted that claim 7 is properly rejected because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, citing *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Solely to advance prosecution of the present application, claim 7 has been canceled.

Accordingly, the rejection under § 101 is rendered moot.

Response To Rejection Under 35 U.S.C. § 102

Claims 1-5 were rejected under 35 U.S.C. § 102(b), as being anticipated by Olsen *et al.* (WO 98/130682-A1, "Olsen"). The Office Action asserted that instant claims 1- 5 are directed to an agent, comprising as an active ingredient, an enzyme, wherein the enzyme comprises the amino acid sequence of SEQ ID NO: 2.

The Office Action alleged that Olsen *et al.* disclose an enzyme comprising the amino acid sequence of SEQ ID NO: 2, and a modified enzyme composition.

The Office Action acknowledged that Olsen *et al.* do not disclose the properties of the enzyme. However, in stating the rejection, the Office Action relied upon the rationale that the instantly claimed enzyme appears to be the same as that disclosed by Olsen *et al.*, and thus the enzyme of Olsen *et al.* must possess the same physical, chemical, and catalytic properties (inherency).

Solely to advance prosecution of the present application, claims 1-5 have been canceled.

Accordingly, the rejection under § 102(b) is rendered moot.

Response To Rejection Under 35 U.S.C. § 103

Claims 1-20 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Shih *et al.* (US 2002/0172989 Al; "Shih") and Olsen, as applied above.

The Office Action contended that Shih discloses a method for digesting infectious prion proteins comprising the step of contacting the prion protein with an enzyme derived from *Bacillus licheniformis*, without preheating the subject at 90°C.

The Office Action further contends that Shih discloses that the proteolytic enzyme be of "any suitable type" and that the choice of specific proteolytic enzyme will affect he choice of temperature that is used for proteolytic degradation, as well as whether the tissue is treated at elevated temperature before exposure to proteolytic enzyme, citing page 3, paragraph [0046]. The Office Action alleges that Shih discloses that such proteolytic enzymes include keratinases, subtilisins, and active fragments of keratinases, citing page 3, paragraphs [0053]-[0054].

However, the Office Action acknowledged that Shih fails to disclose an enzyme comprising the amino acid sequence of SEQ ID NO: 2. In an apparent attempt to rectify this deficiency, the Office Action referred to Olsen to disclose an enzyme comprising the amino acid sequence of SEQ ID NO: 2.

The Office Action asserted that it would have been obvious for one of ordinary skill in the art to have combined the teachings of Olsen with the composition and method of Shih so as to provide an agent, and method using the same, for digesting a pathogenic prion protein. The Office Action asserted that one of ordinary skill in the art would be motivated to make such a combination because it would increase the degrading capacity of the enzyme composition of Shih, thus permitting nutritional use of a material that would otherwise, in the absence of such

treatment, constitute a biological hazard, while further avoiding costs and infrastructure requirements for incineration and disposal of infected or contaminated animal tissue.

In response, Applicants note that in order to establish a *prima facie* case of obviousness, three criteria must be established. First, the references must, in combination, teach each and every limitation of the currently claimed invention, *In re Royka*, 490 F.2d 981, 985 (C.C.P.A. 1974). Second, there must provide sufficient reasons why one of skill in the art would combine the references to arrive at the claimed invention. Finally, there must be a reasonable expectation of success in combining the references. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

In response, Applicants note that Olsen and Shih, separately or in combination, fail to render the claimed invention obvious.

First, Applicants note that, at most, Shih only discloses the keratinase from *Bacillus licheniformis* PWD-1, which as shown in Table 1, has a different molecular weight, a different isoelectric point, and different properties and functions *vis-a-vis* the claimed enzyme.

Shih discloses keratinase PWD-1 derived from *Bacillus licheniformis*, and its use for digesting prion proteins. However, the enzyme used in the present invention is different from keratinase PWD-1, as shown in Table 1 of the present specification.

As discussed in the "Background Art" section of the present specification, when keratinase PWD-1 is used to reduce or digest the pathogenic prion protein by the method disclosed in Shih, two of the treatment steps, a heat treatment as a pretreatment and an enzyme treatment, are necessary. In the Shih method, an apparatus for heating is necessary, and thus it is not easy to carry out the method in common facilities without such an apparatus for heating. Also, the two-step procedure is complicated.

In this regard, Shih discloses that "the term elevated temperature means temperature of at least 35°C" (see paragraph [0031] of Shih), as pointed out by the Office Action (see page 5, lines 3-4 of the Office Action). Shih also discloses as follows:

> "The method can therefore be carried out in various embodiments in which proteolytic susceptibility of infective prion protein in the tissue is enhanced by heating of the tissue to an elevated temperature for subsequent proteolytic enzyme treatment. The elevated temperature in the heating step may be any suitable temperature, e.g., at least 35°C, at least 40°C, at least 60°C, at least 75°C, and/or no more than 150°C (or other lower temperature, as desired), with one illustrative specific temperature range being from about 100°C to about 150°C, and more preferably from about 125°C to about 140°C" (see paragraph [0037] of Shih).

> "As shown in FIG. 1, the digestive effect of keratinase on infectious PrP is evident, particularly when the samples were precooked at 115°C for 40 min (Lanes 3-6). Without precooking (Lanes 7-10), the keratinase was less effective, but keratinase still degraded more than half of the infectious PrP positive material" (see paragraph [0110] of Shih).

In contrast, the enzyme used in the present invention exhibits an excellent activity of digesting a protein highly resistant to denaturation and degradation (particularly a pathogenic prion protein) in comparison with known proteases, such as the keratinase PWD-1. Example 8 and Figure 6 of the present specification clearly show that the mouse pathogenic prion protein was completely digested with the enzyme used in the present invention (i.e., enzyme composition A), but was not digested with the keratinase PWD-1 (i.e., enzyme compositions B and C).

Second, Olsen does not teach the claimed agent. Olsen only discloses the amino acid sequence of subtilisin DY, and does not perform any experiments wherein subtilisin DY is produced or purified, the properties and functions of the claimed protein of instant claims 1-5 clearly are not *necessarily* present in the polypeptide described by Olsen *et al.* Indeed, on page 19, line 10, Olsen *et al.* disclose that "[s]ubtilisin DY has a molecul[ar] weight of 27kDa." The

Office Action clearly fails to consider how post-translational modifications influence protein structure and function. In this regard, Applicants note that as shown in Table 1 of the specification, while the presently claimed enzyme and subtilisin DY may share amino acid sequence, they do not possess an identical chemical structure. It would be illogical to conclude that chemically identical proteins would possess both different molecular weights, as measured by SDS-PAGE, and would also possess different isoelectric points. Further still, Example 9 of the specification discloses that when FERM BP-08487 (the instant strain) and the *Bacillus licheniformis* PWD-1 are cultured in the same medium, under the same conditions, the purified proteins possess different properties with regard to substrate specificity and/or protease activity.

Further, Olsen does not teach or suggest that subtilisin DY can digest a protein highly resistant to denaturation and degradation, such as a pathogenic prion protein. Additionally, as acknowledged by the Office Action, Olsen does not disclose the properties of the enzyme.

Thus, neither Olsen *et al.* nor Shih *et al.* disclose an enzyme claimed by Applicants. Indeed, neither reference even contemplates the use of an enzyme with the particular properties and characteristics of that currently claimed. Thus, Olsen *et al.* and Shih *et al.*, taken either alone or in combination, fail to teach each and every element of the claims, as is required to maintain such a rejection. Accordingly, claims 1-20 are not rendered obvious by the cited references for at least this reason.

Furthermore, Applicants fail to see why a person having ordinary skill in the art would be motivated to combine the references in the manner asserted by the Office Action, since Shih contemplates the use of keratinase from *Bacillus licheniformis* PWD-1 (see Example), which one of ordinary skill in the art would know has the same amino acid sequence as subtilisin DY, disclosed by Olsen. Absent a teaching that subtilisin DY exhibits superior activity in degrading

prions as compared to keratinase from *Bacillus licheniformis* PWD-1, one of ordinary skill in the art would not reasonably consider using subtilisin DY in place of keratinase from *Bacillus licheniformis* PWD-1 in the method of Shih, even considering that both have the same amino acid sequence. Accordingly, one of ordinary skill in the art would not reasonably be lead to combine the references in the manner asserted by the Office Action.

Thus, Shih and Olsen fail to render the instant claims obvious for at least the reasons discussed above.

Claims 1-5, 7-8, and 12-16 have been canceled. Accordingly, the rejection is rendered moot with regard to claims 1-5, 7-8, and 12-16.

Reconsideration and withdrawal of the rejection under § 103(a) is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of pending claims 6, 9, 10, 11 and 17-42 of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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